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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Thomas D. Madden et al.
Application No.	:	09/896,812
Filed	:	June 29, 2001
For	:	LIPOSOMAL ANTINEOPLASTIC DRUGS AND USES THEREOF

Examiner	:	Gollamudi S. Kishore
Art Unit	:	1615
Docket No.	:	480208.408

DECLARATION OF THOMAS D. MADDEN, Ph.D.
PURSUANT TO 37 C.F.R. §1.132

I, Thomas D. Madden, Ph,D. declare as follows:

1. I currently hold the position of Senior Director, Technology Development & Licensing, at Inex Pharmaceuticals, located in Burnaby, British Columbia, Canada, the assignee of the above-identified application (the "application"), and I am a co-inventor of the subject matter disclosed therein. I have conducted and supervised research in the field of liposomal drug delivery for over twenty years. A copy of my curriculum vitae is attached.

2. I am familiar with the content of the application, and I have reviewed the Office Action mailed October 3, 2005 and the prior art references cited therein, namely U.S. Patent No. 6,110,491 ("Kirpotin") and U.S. Patent No. 5,543,152 ("Webb"). In this Office Action, the Examiner suggests that the skilled artisan would be motivated to produce a liposomal vinorelbine formulation having a the high drug:lipid ratio of 0.1-0.5:1 (w/w) based upon these references. I submit this Declaration as evidence that the claimed liposomal vinorelbine formulations are not obvious and that the

claimed liposomal vinorelbine formulations offer surprising advantages over the prior art. In addition, I submit that the skilled artisan would not have been motivated to produce the claimed liposomal vinorelbine formulations in light of these references.

3. It is my experience and knowledge that the optimal drug:lipid ratio varies for different drugs. The specific liposome components (*e.g.*, lipids), the particular drug, and the particular drug:lipid ratio are all variable features of liposomal formulations, each of which contributes to the pharmacokinetic properties of a liposomal drug formulation. Furthermore, these properties are not independent of each other, as the characteristics of a particular drug (*e.g.*, solubility, half-life, and size) will contribute to determining the best combination of these features. Accordingly, the identification and selection of preferred liposomal formulations for any particular drug requires considerable effort and experimentation and cannot be readily predicted by analogy to other drugs or formulations. Therefore, I do not believe that the claimed liposomal vinorelbine formulations, having a high drug:lipid ratio with resulting enhanced drug retention, can be considered obvious over the description of liposomal formulations containing a different drug, particularly when those liposomal drug formulations are described as having a substantially broader range of drug:lipid ratio (as described in Webb) and a general reference to liposomal vinorelbine formulations (as described in Kirpotin).

4. I further submit that the skilled artisan would not be motivated by the teachings of Webb or Kirpotin to produce a liposomal vinorelbine formulation having a high drug:lipid ratio. This invention is based, in part, on the surprising discovery by Appellants that, at high drug:lipid ratios, vinorelbine precipitates within a liposome, leading to increased drug retention within the liposome. This contravenes the conventional wisdom in the art, which was that higher drug:lipid ratios lead to increased drug leakage from liposomes. Specifically, drug loading and retention within liposomes is most commonly achieved using an ion gradient, such as a pH gradient, as disclosed in Webb, Kirpotin, and the instant application. Such ion gradients can drive drug

redistribution across the liposomal bilayer, where the drug is an ionizable compound, such that a substantial drug concentration gradient is achieved (as predicted by the Henderson-Hasselbach equation). However, drug accumulation within the liposomal interior depletes the initial ion gradient such that the residual gradient after loading is less than the initial ion gradient. As this residual gradient is required to retain the loaded drug within the liposomes, and to slow drug release from the liposomes in vivo, a high residual gradient is preferred. The extent to which the initial ion gradient is depleted by drug loading will be dependent on the drug:lipid ratio with formulations having a high drug:lipid ratio having a lower residual ion gradient. Accordingly, as enhanced drug retention is considered a desired feature in liposomal drug formulations, the skilled artisan would not be motivated to use high drug:lipid ratios, such as those associated with the claimed liposomal vinorelbine formulations, as this would be expected to result in a lower residual ion gradient and faster drug release in vivo. It is only the inventors who have shown that at high drug:lipid ratios, vinorelbine precipitates within the liposomes thereby providing for slow drug release even in the presence of a lower residual ion gradient. In summary, I note that the advantages associated with the claimed high drug:lipid ratio liposomal vinorelbine formulations were not recognized or described in the prior art references and could not be predicted or expected based upon the teachings of these references.

I hereby declare that all statements made herein are, to my own knowledge, true and that all statements made on information or belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the captioned patent application or any patent issued therefrom.

Date October 30th 2006

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